What's New in Syphilis*

C. W. BARNETT, M.D., *San Francisco*

PENICILLIN is still the newest thing in syphilis. It is not actually very new as it has been in use for more than four years, but since the evaluation of antisyphilitic therapy is a very slow, tedious and uncertain process, we are just beginning to learn what can be expected of penicillin.

Evaluation of therapy in syphilis must be carried out on a different basis than in most other diseases because it has to be done in reverse. If a patient with syphilis is treated and subsequently remains well for a year or two, there is no evidence that he is cured, but if any manifestations of the disease reappear, it is clear that the treatment has failed. Arrest or cure in syphilis cannot be claimed until a patient has died without having developed any further evidence of the infection. So, in order to draw conclusions within a reasonable period of time, we are forced to compare the effectiveness of different treatment schemes according to the relative incidence of failure.

Early detection of treatment failure is possible only in early syphilis and the clinical evaluation of any new antisyphilitic agent must be initiated at this stage of the disease. The recurrence of lesions of syphilis, or of strongly positive serologic tests after previous negativity, the persistence of strong positive tests for a year after treatment or the development of clinical or serologic evidence of nervous system involvement, all indicate failure. The frequency of such events after the treatment of syphilis with penicillin is the principal basis for the determination of the value of penicillin and of the most effective methods for its administration.

The most extensive investigation of penicillin in early syphilis has been carried out under the direction of the National Research Council and later the National Institute of Health with the cooperation of the army and the navy and some forty civilian clinics scattered throughout the United States. About a year ago, the material from this investigation was summarized and it appeared that the position of penicillin in the treatment of syphilis was settled. About 10,000 patients with early syphilis had been treated, with a variety of treatment schemes, and had been observed for slightly over a year. The results led to the development of certain principles of penicillin therapy upon which most of our subsequent treatment has been based.

In brief, these principles were that the total dose should be at least 2.4 million units, that the injections should be given at intervals of not over three hours, that the treatment should occupy a period of not less than seven days and that small amounts of arsenoxide and bismuth should be given in addition, since this was shown to decrease markedly the incidence of treatment failure with only a moderate increase in risk.

Recently the results of this investigation have been reviewed again with the number of cases increased to 15,000 and the period of observation to almost two years. The conclusions reached as a result of this re-survey are indeed startling. Everything that we thought we knew about the treatment of syphilis with penicillin last year now appears to be wrong. The total dose is of little consequence, the same results being obtained with anything from 1.2 to 10 million units. It makes no difference whether the injections are given at intervals of two, four or six hours, and the time of treatment may be four, seven or fifteen days. Of still greater importance is the demonstration that the addition of arsenic or bismuth, either combined or separately, adds nothing to the effectiveness of penicillin therapy, and since it does definitely augment the risk, the combination of these drugs with penicillin should be abandoned in the future.

The most alarming conclusion from this treatment survey, however, is that the total incidence of failure after penicillin therapy is almost 30 per cent no matter what scheme of treatment is used. This is a poor record in comparison with many of the older treatment regimes using arsenic and bismuth, and the question arises whether or not we can justify the use of penicillin when it results in a failure rate of such magnitude. I think we can on the basis of two factors that must be considered but cannot be expressed in figures.

The first of these is toxicity. Penicillin is completely innocuous and thereby differs from all other antisyphilitic agents which are essentially dangerous. Secondly, penicillin treatment can be completed within a period of a few days so that practically every patient who starts the therapy completes it.

The only type of treatment that competes with penicillin in time of administration is intensive arsenotherapy where curative doses of arsenic are administered in a period of five to ten days. The risk of this treatment is exceedingly high and although the failures are few among those who survive, the overall death-rate of 1/200 practically eliminates this type of therapy.

On the other hand, experience has shown that the older treatments fail largely because only about 35 per cent of those who start ever go on to completion. Those who complete the older treatment are probably better off than those who take penicillin but for those who fall by the wayside, penicillin would have been infinitely better.

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Associate Professor of Medicine, Stanford University School of Medicine, San Francisco.

On the grounds, therefore, that penicillin therapy can be completed in every case in which it has been started and that its administration is practically devoid of danger, I think it is still the treatment of choice in early syphilis in spite of its high rate of failure. This opinion is based partly on the fact that an initial failure in treatment does not indicate the impossibility of final cure. There is no evidence that syphilis can become resistant to penicillin and the great majority of patients who have required retreatment have responded perfectly well to subsequent courses of penicillin and have, for the most part, remained permanently well. However, because of the frequency of relapse after penicillin, it is vital that patients treated with it be followed with great care. They should be examined physically for lesions of the skin and mucous membranes at intervals of not over one month for the first year and every few months after that for several years. They should also have periodic serologic tests, preferably by some quantitative technic, taken at the time of their physical examinations.

In late syphilis, we know less about penicillin therapy than in early syphilis. It appears to be quite useful in neurosyphilis of various kinds and is of particular value because it not infrequently is effective in cases which would be expected to respond only to fever therapy with its very much greater risk.

Penicillin seems to be better than anything we have ever had for the treatment of syphilis during pregnancy. It will almost invariably protect the child regardless of the duration of the pregnancy or of the stage of the infection in the mother. It is probably not indicated in late latent syphilis and we would not expect it to have any great effect on the Wassermann reaction because in its widespread use in late neurosyphilis, it has been shown to be relatively ineffective in producing a negative serologic test in the blood. In particular it should not be used in a final attempt to reverse a blood Wassermann that has remained positive in a patient who has already had adequate therapy of the conventional type.

DISCUSSION AND QUESTIONS AND ANSWERS

I have more questions here than I can answer in detail and a number of which I am afraid I cannot answer at all. Several of them concern the effect of penicillin in oil and wax. I did not mention this because of the limited experience we have had with it, but one of the most encouraging results of the penicillin in syphilis study is that penicillin in oil and wax appears to be somewhat more effective than does soluble penicillin. In this study, the total dose was 4.8 million units or more, usually given in daily doses of 600,000 units each. A more prolonged period of observation may change this impression, however, as it did in the case of the soluble preparation.

There are several questions about the time of retreatment after an initial failure. Retreatment should be started as soon as the failure is evident. If there is only a serologic relapse, it must be confirmed by the examination of another specimen of blood, before treatment is begun. If the only evidence of failure is the persistence of a positive serologic test, the treatment should not be repeated unless a strongly positive test persists for at least a year. Retreatment may be carried out with penicillin in augmented dosage, with conventional arsenic and bismuth therapy, or possibly some combination of the two.

The questions concerning the time that must elapse before sexual intercourse or marriage may be permitted after penicillin therapy are difficult to answer. Because of the high incidence of relapse, there is no period of time that will eliminate all possibility of transmission. Most infectious relapses occur within the first six months after therapy and most of them are preceded or accompanied by serologic relapses. Therefore, if we are to be reasonable about it, and will admit the impossibility of absolute safety, it seems to me that intercourse may be permitted with very little risk of transmission in the case of a patient whose blood has become negative and has remained so, but not for the first six months after treatment has been completed. If the patient is a male, a condom should be used, since the infection is occasionally transmitted by the seminal fluid in the absence of visible lesions. If the patient is female, the sexual partner should use chemical prophylaxis after each intercourse as an added protection.

Several physicians have asked how soon the blood will become negative after penicillin treatment. Usually two to three months elapses between the institution of therapy and the reversal of the blood tests. Even though the treponema pallidum has been eradicated by treatment, reagin will persist in the blood for some time and one should not expect an immediate reversal. Occasionally, as long as a year elapses before the blood becomes negative although quantitative tests will usually reveal a steady decline in serologic titer.

I have one question about the published results of the recent re-evaluation of penicillin in syphilis. The material was presented at a meeting of the Syphilis Study Committee of the National Institute of Health in Washington, D. C., on April 17, 1947. It has not been published as yet, and as to whether or not it will be I have no information.